Besponsa™ (inotuzumab ozogamicin)
(Intravenous)

-E-

Document Number: IC-0453

Last Review Date: 12/01/2020
Date of Origin: 05/01/2019
Dates Reviewed: 05/2019, 12/2019, 12/2020

I. Length of Authorization

Coverage will be provided for 6 months (for up to a maximum of 6 cycles) and may not be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Besponsa 0.9 mg powder for injection: 7 vials per 21 days

B. Max Units (per dose and over time) [HCPCS Unit]:

Cycle 1

- 27 billable units (2.7 mg) on Day 1, 18 billable units on Days 8 and 15 of a 21 to 28-day cycle

Subsequent Cycles (maximum of 5 cycles)

- 27 billable units (2.7 mg) on Day 1, 18 billable units on Days 8 and 15 of a 28-day cycle for up to 2 cycles
- 18 billable units (1.8 mg) on Day 1, Day 8, and Day 15 of a 28-day cycle for up to 3 cycles

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Baseline electrocardiogram (ECG) is within normal limits; **AND**
- Patient has not previously received inotuzumab ozogamicin; **AND**
- Patient has CD22-positive disease; **AND**

B-Cell Precursor Acute Lymphoblastic Leukemia (ALL) † [1-3]

- Patient aged 18 years or older; **AND**
  - Patient has relapsed or refractory disease; **AND**
    - Used as single agent therapy; **AND**
      - Patient is Philadelphia chromosome (Ph)-negative; **OR**

- Patient is Philadelphia chromosome (Ph)-positive and failed previous therapy (i.e., intolerant or refractory) with a tyrosine kinase inhibitor (e.g., imatinib, dasatinib, ponatinib, nilotinib, bosutinib, etc.); **OR**

- Used in combination with mini-hyper CVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine); **AND**
  - Patient is Philadelphia chromosome (Ph)-negative

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendium Recommended Indication(s)

IV. Renewal Criteria[1]

Coverage cannot be renewed.

V. Dosage/Administration[1]

Indication	Dose
B-Cell Precursor ALL	**Cycle 1:** • 1.8 mg/m^2 total per cycle, administered as 3 divided doses on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2) • Cycle 1 is 3 weeks in duration, but may be extended to 4 weeks if the patient achieves CR or CRi, and/or to allow recovery from toxicity **Subsequent Cycles (cycles are 4 weeks in duration):** <u>CR or CRi achieved</u> • 1.5 mg/m^2 total per cycle, administered as 3 divided doses on Day 1 (0.5 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2) <u>Did not achieve CR or CRi</u> • 1.8 mg/m^2 total per cycle, administered as 3 divided doses on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2) • Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment. **Patients proceeding to HSCT:** • Recommended duration of treatment is 2 cycles • A third cycle may be considered for those patients who do not achieve CR or CRi and MRD negativity after 2 cycles **Patients not proceeding to HSCT:** • Additional cycles of treatment, up to a maximum of 6 cycles, may be administered
CR (complete remission); CRi (complete remission with incomplete hematologic recovery); HSCT (hematopoietic stem cell transplant); MRD (minimal residual disease)	

VI. Billing Code/Availability Information

<u>HCPCS Code</u>:

- J9229 – Injection, inotuzumab ozogamicin, 0.1 mg (effective 1/1/19)

NDC:

- Besponsa 0.9 mg lyophilized powder in single-dose vial: 00008-0100-xx

VII. References (STANDARD)

1. Besponsa [package insert]. Philadelphia, PA; Pfizer Inc., March 2018. Accessed October 2020.
2. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med. 2016 Aug 25;375(8):740-53.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) inotuzumab ozogamicin. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed October 2020.
4. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia [published correction appears in Leukemia. 2019 Mar 7;:]. Leukemia. 2019;33(4):884–892. doi:10.1038/s41375-018-0265-z.
5. Palmetto GBA, LLC. Local Coverage Article: Billing and Coding: Chemotherapy (A56141). Centers for Medicare & Medicaid Services, Inc. Updated on 05/26/2020 with effective date 04/30/2020. Accessed October 2020.

VIII. References (ENHANCED)

1e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Acute Lymphoblastic Leukemia, Version 1.2020. National Comprehensive Cancer Network, 2020. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed October 2020.

2e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Pediatric Acute Lymphoblastic Leukemia, Version 1.2021. National Comprehensive Cancer Network, 2020. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed October 2020.

3e. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017; 376:836-847.

4e. Martinelli G, Boissel N, Chevallier P, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. J Clin Oncol. 2017 Jun 1;35(16):1795-1802.

5e. Maude S, Laetsch T, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018; 378:439-448.

6e. Jabbour E, Ravandi F, Kebriaei P, et al. Salvage Chemoimmunotherapy With Inotuzumab Ozogamicin Combined With Mini-Hyper-CVD for Patients With Relapsed or Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Phase 2 Clinical Trial. JAMA Oncol. 2018;4(2):230-234. doi:10.1001/jamaoncol.2017.2380.

7e. Magellan Health, Magellan Rx Management. Besponsa Clinical Literature Review Analysis. Last updated October 2020. Accessed October 2020.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Articles (LCAs), and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCA/LCD):

Jurisdiction(s): J & M	**NCD/LCA/LCD Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/lcd-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; RFS = relapse free survival; ASCT = allogeneic stem cell transplantation; MRD = minimal residual disease; TKI = tyrosine kinase inhibitor; Ph = Philadelphia chromosome; VOD = veno-occlusive disease

B-Cell Precursor Acute Lymphoblastic Leukemia (ALL)

Relapsed or Refractory Disease – CD22-positive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Inotuzumab ozogamicin	1 preferred for Philadelphia-chromosome negative B-ALL 2A other for Philadelphia-chromosome positive TKI intolerant or refractory	Yes	Phase 3 (INO-VATE), randomized, open-label	Standard of care (SOC): • FLAG • HiDAC-based regimen	CR and OS	Relapsed or refractory CD22-positive Ph+ or Ph-negative ALL in patients due for first or second salvage treatment. Ph+ patients were required to have failed treatment with at least 1 TKI and standard chemotherapy	• Patients receiving inotuzumab ozogamicin versus standard care achieved higher response, MRD-negativity rates, and prolonged PFS and OS
Inotuzumab ozogamicin + mini-hyperCVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine)	2A other	No	Phase 2, single-arm	N/A	ORR OS	Relapsed or refractory disease	• In patients with relapsed or refractory ALL, the combination of inotuzumab with low-intensity mini-HCVD chemotherapy demonstrated an ORR 78% with 44% of patients proceeding to ASCT.

Blinatumomab	1 preferred for Philadelphia-chromosome negative B-ALL 2A other for Philadelphia-chromosome positive TKI intolerant or refractory B-ALL	Yes (Not restrictive of Ph-status)	Phase 3 (TOWER), randomized	Standard of care: • FLAG ± anthracycline-based regimen • HiDAC-based regimen • High-dose methotrexate-based regimen • Clofarabine-based regimen	OS	Relapsed or refractory disease	• Treatment with blinatumomab resulted in significantly longer OS than chemotherapy
Blinatumomab	1 preferred for Philadelphia-chromosome negative B-ALL 2A other for Philadelphia-chromosome positive TKI intolerant or refractory B-ALL	Yes (Not restrictive of Ph-status)	Phase 2 (ALCANTARA), open-label, single-arm	N/A	CR or CRh	After imatinib and at least one second-generation or later TKI	• Blinatumomab demonstrated antileukemia activity in high-risk patients with Ph+ ALL who had relapsed or were refractory to TKIs
Tisagenlecleucel	2A other for patients < 26 years and with refractory disease or ≥ 2 relapses	Yes for patients up to 25 years of age with B-cell ALL that is refractory or in second or later relapse	Phase 2 (ELIANA), single-cohort	N/A	ORR	Relapsed or refractory disease	• Tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects
Chemotherapy (hyper-CVAD, clofarabine, etc.)	2A						

Induction Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Inotuzumab ozogamicin + mini-hyperCVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine)	2A other	No	No clinical literature to support use.				

B-Cell Pediatric Acute Lymphoblastic Leukemia (ALL)

Relapsed or Refractory Disease – CD22-positive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Inotuzumab ozogamicin	2A	No	Retrospective study	N/A	-----	Relapsed or refractory ALL	• Inotuzumab ozogamicin is well-tolerated and effective for children with relapsed ALL demonstrating a complete remission rate of 67%.